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Quantitative electroencephalogram utility in predicting conversion of mild cognitive impairment to dementia with Lewy bodies☆

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ABSTRACT

Mild cognitive impairment (MCI) as a precursor of dementia with Lewy bodies (DLB) is the focus of recent research, trying to explore the early mechanisms and possible biomarkers of DLB. Quantitative electroencephalogram (QEEG) methods are able to differentiate early DLB from Alzheimer's disease (AD). The aim of the present study was to assess whether QEEG abnormalities, characterized by dominant frequency <8 Hz and dominant frequency variability >1.5 Hz, typical of early DLB, are already present at the stage of MCI and to evaluate whether EEG abnormalities can predict the development of DLB. Forty-seven MCI subjects were followed for 3 years. EEG recordings were obtained at admission and at the end of the study. At the end of follow-up, 20 subjects had developed probable DLB (MCI-DLB), 14 had probable AD (MCI-AD), 8 did not convert to dementia, 5 developed a non-AD/DLB dementia. One hundred percent of MCI-DLB showed EEG abnormalities at admission. Ninety three percent of MCI-AD maintained a normal EEG throughout the study. QEEG may represent a powerful tool to predict the progression from MCI to DLB with a sensitivity and specificity close to 100%.

1. Introduction

The early identification of dementia is becoming increasingly important, as it is likely that it is during this time period, before the manifestation of significant pathophysiological change that disease modifying treatments will have their biggest impact. Dementia is generally preceded by an early preclinical phase, which progresses to mild cognitive impairment (MCI) and finally to dementia (Albert et al., 2011). The observations and evaluation of MCI patients through neuropsychological tools designed to assess different cognitive domains (such as memory, executive functions, and visuospatial skills) commonly applied to patients with dementia, allow the definition of 2 main MCI subtypes: amnestic MCI (aMCI), which presents with dominant memory function impairment; and nonamnestic MCI (naMCI), which presents with prominent impairment of cognitive domains other than memory, and includes attention, language, executive functions, visuospatial skills.

In both MCI subtypes, the cognitive impairment can be restricted only to a specific domain (e.g., memory and attention), defining the so-called single-domain MCI, or can present as a combination of dysfunctions in more than 1 cognitive domain, defining the so-called multiple domain MCI (Winblad et al., 2004).

It has been proposed that the different subtypes of MCI are associated with progression to different dementia types.

Specifically, patients with amnestic MCI are considered more likely to progress to Alzheimer's disease (AD) (Petersen et al., 2001), whereas patients with naMCI are more likely to progress to a non-AD dementia, including, for example, dementia with Lewy bodies (DLB) (Boeve, 2012).

Currently, great efforts are being put toward the early identification of preclinical, biological, clinical, laboratory markers which are able to predict the conversion of MCI to AD (Sperling et al., 2011).

An example of a successful biomarker of conversion from MCI to AD is the analysis of proteins present in the cerebrospinal fluid (CSF) and in particular total tau (tau), phosphorylated tau (P-tau), and the 42-amino-acid isoform of amyloid-β_{1-42} ($A\beta_{42}$) (Parnetti et al., 2012). Similarly, structural and functional neuroimaging

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studies have provided biomarkers for the conversion of MCI to AD (Tosun et al., 2013).

A further promising approach to assess the conversion of MCI subjects to AD subjects or to study the progression of AD from mild to more pronounced stages of dementia is the recording of resting state eyes-closed electroencephalographic (EEG) rhythms.

Cortical sources of resting state EEG rhythms in mild AD patients are sensitive to the disease progression at the early stage over 1 year (Babiloni et al., 2013). In particular, follow-up EEG recordings (Babiloni et al., 2013) have demonstrated that alterations of EEG cortical rhythms characterized either by increased power of widespread delta sources and decreased power of alpha and posterior beta (13–20 Hz) sources in mild AD patients or by decreased power of posterior alpha sources in amnestic MCI subjects correlate with cognitive decline (Babiloni et al., 2013, 2014).

However, although MCI as a prodromal condition for AD is a well studied and characterized condition, (Petersen et al., 2001), MCI associated with Lewy body disease (including DLB and PDD), which represents the second most common form of neurodegenerative dementia and associated with highly distressing behavioral symptoms (McKeith et al., 2005) appears to be less typified in literature (Auning et al., 2011; Burn and Barker, 2013; Litvan et al., 2011).

EEG has extensively been studied as a possible tool to assess the presence of dementia (Breslau et al., 1989; Briel et al., 1999; Giaquinto and Nolfe, 1986), and in Consensus criteria for the diagnosis of DLB, EEG abnormalities are described among the supportive features for the diagnosis of DLB (McKeith, 2005).

Several studies suggested that EEG analyzed with quantitative methods is able to differentiate with high specificity and sensitivity, DLB from AD from the very early stages of disease (Andersson et al., 2008; Bonanni et al., 2008; Franciotti et al., 2006; Walker et al., 2000), and these alterations of electrocortical arousal are highly correlated with the presence of fluctuating cognition (Andersson et al., 2008; Bonanni et al., 2008; Franciotti et al., 2006; Walker et al., 2000), a core symptom for the diagnosis of DLB, which among the various clinical features proposed for DLB diagnosis, has been demonstrated to be the most specific (Tiraboschi et al., 2006).

In contrast, in AD patients EEG abnormalities are typically represented by slowing of the background activity, which is reported either as widespread on the scalp derivations or as more prominent in temporal derivations (Valladeres-Neta et al., 1995).

In our previous systematic study (Bonanni et al., 2008), however, when attempting to differentiate EEG characteristics of DLB from those found in AD patients, the highest statistical yields were obtained in the comparison of dominant frequency and variability of the dominant frequency measured on recordings from posterior derivations. No statistical differences were found in temporal derivations between the 2 disease groups (Web material 1).

This finding can be explained by the presence of delta and/or theta activity in temporal derivations of both DLB and AD patients, in line with the results widely reported in literature (Babiloni et al., 2013).

Although AD patients present with an EEG pattern, characterized in posterior derivations by a dominant frequency in the alpha band prevalent in >55% of the analyzed EEG epochs and a dominant frequency variability <1.2 Hz, DLB patients present with derangement of EEG background activity in occipital derivations, characterized by dominant frequency in frequency bands lower than alpha (i.e., pre-alpha, theta, and delta) with dominant frequency variability >1.2 Hz and a frequency prevalence of pre-alpha in >40% of the analyzed EEG epochs and a frequency prevalence of alpha rhythm in <32%, as detailed in (Bonanni et al., 2008).

The aim of the present study is 2-fold: (1) to assess whether EEG characteristics described in our previous work as typical of early DLB and/or PDD are already present in MCI subjects; (2) evaluate whether possible EEG abnormalities in MCI individuals can predict the subsequent development of DLB.

2. Methods

2.1. Patients

The study sample was recruited among the new referrals in the year 2008 to the Memory Clinic and Movement Disorder Centre, Neurology Clinic of the University G. d'Annunzio of Chieti-Pescara, serving a population of 1,200,000 inhabitants of Abruzzo region, central Italy.

Given that the principal aim of the study was to assess the predictive value of EEG in the early diagnosis of DLB, we enriched our study sample by the inclusion of MCI subjects who had at least 1 core or suggestive DLB symptom (McKeith et al., 2005). Therefore, based on DLB prevalence in our dementia center (Bonanni et al., 2013) we selected 3 MCI subjects with 1 core or suggestive DLB symptom, according to DLB diagnostic criteria (McKeith et al, 2005) for every MCI subject without any DLB symptom.

A total of 99 subjects referred to our center because of subjective complaint of cognitive impairment. Forty-seven subjects were addressed to our attention by the general practitioners who had noticed changes in the cognitive performances of their patients. Concerns about cognition were expressed by the individual's family members in 30 cases and by the individuals themselves in the remaining 22 cases.

The individuals were categorized as MCI according to the criteria proposed by Petersen et al. (1999), including the presence of subjective complaint of memory dysfunction; pathologic scores in memory tests for age and educational level, underlying a memory impairment not interfering with the activities of daily living and normal general cognitive function.

International criteria for DLB diagnosis were applied to select MCI subjects with and without 1 core or suggestive feature of DLB.

Any subjects who had a prior history of PD or PD symptoms longer than 1 year before admission to the study were excluded from the study.

Furthermore, the international diagnostic criteria for AD (McKhann et al., 1984), vascular dementia (Roman et al., 1993), DLB (McKeith et al., 2005), and frontotemporal dementia (McKhann et al., 2001) were applied to exclude the presence of overt dementia.

All the subjects were tested with a composite battery of tests for cognition, including the Mini Mental State Examination (MMSE), the Clinical Dementia Rating (Morris et al., 1993), the Global Deterioration Scale (Reisberg et al., 1982), and the Dementia Rating Scale-2 (DRS-2) (Jurica et al., 2001).

An MMSE score of >24, a global Clinical Dementia Rating rating of stage 0.5 (defined as "questionable impairment"), a Global Deterioration Scale score of 2–3, and a DRS-2 score >123 were considered necessary to MCI diagnosis.

The presence of accompanying illnesses including neoplasia, blood hypertension, diabetes, obesity, malnutrition (vitamin deficiency), thyroidal diseases; alcohol present or past abuse, use of antidepressants, anticonvulsants, and benzodiazepines; depression as assessed by the Geriatric Depression Scale (Yesavage et al., 1982-1983) (score >5) were considered as exclusion criteria.

A total of 47 of 99 individuals fulfilled the criteria for MCI and were admitted to the study. Among them 21 had 1 core or suggestive feature of DLB (Fig. 1 summarizes the study design).

For comparison 50 DLB and 50 AD patients in mild stage (disease duration: 1–2 years), matched with MCI subjects for age and educational level were randomly selected from our dementia register. The diagnosis of DLB or AD was made according to international criteria (McKeith et al., 2005; McKhann et al., 1984). In addition, 50 age and educational level-matched healthy individuals, with no either subjective or objective cognitive deficits and no